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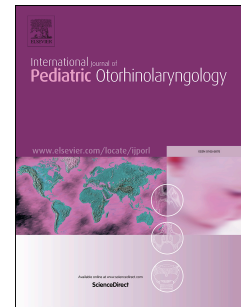
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Childhood nontuberculous mycobacterial lymphadenitis –observation alone is a good alternative to surgery

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Short running title: NTM lymphadenitis in children

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Abstract

Objective

Cervicofacial lymphadenitis caused by nontuberculous mycobacteria (NTM) is commonly treated with surgery or antimicrobial therapy. The aim of this study was to analyze the utility of our new blood-based diagnostic method and the treatment protocol, surgery or observation alone, in NTM lymphadenitis in children.

Methods

All patients under 16 years of age with cervicofacial NTM lymphadenitis diagnosed and treated at Children's Hospital or at the Department of Otorhinolaryngology, Helsinki University Hospital (Helsinki, Finland) in 2007-2017 were retrospectively reviewed.

Results

Fifty-two patients, 33 (63%) of whom were girls, were included in the study. The median age at initial presentation of the NTM lymphadenitis was 2.9 years. The novel blood-test had been performed on 49 (94%) of the patients and in all of them it was indicative of NTM infection. A sample for mycobacterial culture was available from 34 patients, and *Mycobacterium avium* was the most common species detected. Most patients (n=33, 63%) were treated conservatively with observation alone. Of these, nine patients (27%) did not develop a skin fistula, and the lymphadenitis resolved without drainage.

Conclusions

The novel blood test is clinically feasible method for diagnosing childhood cervicofacial NTM lymphadenitis noninvasively. Observation alone is a good alternative to surgery, without the risk of complications.

Keywords: Non-tuberculous mycobacteria, lymphadenitis, children

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1. Introduction

Nontuberculous mycobacteria (NTM) are abundant microbes found in soil and water. NTM and *Mycobacterium tuberculosis* (MTB) are closely related. Therefore, Bacillus Calmette-Guérin (BCG) vaccine prevents NTM infections as well as childhood tuberculosis (TB). In Finland, universal BCG vaccinations were discontinued in 2006. Consequently the BCG coverage of infants dropped from >98 % to an estimated 6%, and childhood NTM infections increased drastically.¹ A similar increase has been observed previously, e.g. in Sweden.²

In children, NTM infection typically affects cervicofacial lymph node(s). The clinical presentation is distinctive; a painless lump in the neck or parotid area, which in weeks/months turns into a red/purple lesion that eventually can burst and drain. Typically, the child is otherwise asymptomatic.

Due to lack of conclusive studies, the treatment of choice for NTM lymphadenitis remains undefined. For decades, the gold standard of treatment for NTM lymphadenitis has been surgical removal of the infected lymph node. Another widely used approach is a lengthy treatment with antibiotic combinations. In a randomized controlled trial comparing these treatment options, cure was achieved earlier with surgery. However, surgical complications were seen in 28% and adverse effects of antimicrobials in 78% of the patients.³ There is increasing evidence from observational studies that the infection resolves spontaneously without any treatment. In 2008, Zeharia et al. published a study with 92 children treated with a conservative, observation-only approach.⁴ The infection resolved without any complications within one year in all of the patients. In a recent meta-analysis of 1951 children treated with surgery, antibiotics, or observation alone, complete excision had the highest mean cure rate, but also a 2% risk of a serious complication, permanent facial nerve palsy. Furthermore, antimicrobial treatment had more side-effects, but no benefits compared with observation alone.⁵ However, only 8% of the patients were in the observation-only group.

In our hospital, in-house modifications made to the commercial T-SPOT.TB blood test include an additional purified protein derivative (PPD) antigen stimulation.⁶ Currently, the modified test is a routine, noninvasive, investigation for children with suspected NTM lymphadenitis. Our treatment approach for childhood NTM lymphadenitis is either removal of the infected lymph node(s) or observation alone.

In this study we evaluate the outcomes of a single tertiary-care hospital treatment protocol – surgery or observation only – of cervicofacial NTM lymphadenitis in children. The aim was to describe the variety of clinical symptoms and healing process, especially drainage duration in our population, and whether either of the protocols was superior when comparing the outcome, symptoms or amount of complications, in order to change our approach accordingly.

2. Materials and Methods

We conducted a retrospective review of medical records of all patients under 16 years of age with cervicofacial NTM lymphadenitis diagnosed and treated at the Children's Hospital and at the Department of Otorhinolaryngology – Head and Neck Surgery, Helsinki University Hospital (Helsinki, Finland) from January 1, 2007 to May 31, 2017. The search was based on the ICD-10 diagnosis code for cervicofacial lymphadenitis (L04.0) and other mycobacterial infection (A31.9 and A31.89).

The diagnosis of NTM lymphadenitis was defined as 1) a typical clinical history and appearance of cervicofacial NTM lymphadenitis and 2) a positive modified T-SPOT.TB test result and/or NTM detected in cultures. Typical clinical appearance was defined as cervicofacial lymphadenitis in an otherwise healthy child, starting with a painless lump in the neck or parotid area and proceeding to a red/purple lesion, which could burst and drain.

2.1 Diagnostic protocol

In Finland, children with prolonged lymphadenopathy are referred to a pediatrician or specialist in otorhinolaryngology (ORL). If NTM lymphadenitis is suspected based on clinical history and findings, our primary diagnostic test is a novel modified T-SPOT.TB blood test.

Briefly, the commercial T-SPOT.TB is an *in vitro* interferon gamma release assay (IGRA) test used to diagnose TB infection. First, peripheral blood mononuclear cells (PBMCs) containing T cells are separated from a blood sample. Second, PBMCs are stimulated in a well with a specific antigen (i.e. peptide mixture). If the T cells are sensitized to the antigen (i.e. the patient carries infection), they secrete interferon gamma (INF- γ). Third, the secreted INF- γ is captured in the well and visually detected as spots that are enumerated. If the number of spots (i.e. individual reacting T cells) exceeds the set cut-off value, the antigen reaction is considered positive. Because antigen stimulations are performed in separate wells, the reaction for each antigen can be measured separately.

The commercial test contains antigens that are MTB-specific. Uniquely, our modified T-SPOT.TB test includes additional stimulation with PPD antigen. PPD is commonly used in the tuberculin skin test (TST) and contains a mixture of proteins that are present in MTB, *Mycobacterium bovis* BCG, and NTM. Therefore, a positive antigen reaction to PPD and negative reaction to MTB-specific antigens in the test can indicate either BCG vaccination or NTM infection.

After the 2006 BCG vaccine policy change and the subsequent increase in childhood NTM infections, the test appeared promising and useful for diagnosing NTM lymphadenitis in non-BCG-vaccinated children (estimated sensitivity of 100% and specificity of 81%).⁶ In our hospital the test became a part of the diagnostic scheme for childhood NTM lymphadenitis; the rationale is that in a non-BCG-vaccinated child presenting with a typical clinical and sonographic appearance of NTM lymphadenitis, a positive reaction to PPD alone indicates NTM infection. If the clinical presentation

is unusual, bacterial typing is required, or the modified T-SPOT.TB test is negative, or if a sample can be obtained easily from a draining fistula, further investigations include mycobacterial cultures and/or histological examination.

2.2 Treatment protocol

In our hospital, after diagnosis of NTM cervicofacial lymphadenitis, the natural course of the disease and the treatment options are discussed with the parents. Infected lymph nodes are surgically removed if the risk of surgical complication is low (e.g. facial nerve damage) and the parents favor surgery. If a bacterial or histological specimen is needed due to unusual clinical presentation and/or unconfirmed laboratory test, fine needle biopsy or surgery is warranted. If the risk of surgical complications is high (e.g. lymph nodes in the parotid area or near facial nerve) or the parents do not favor surgery, the patients are followed without antimicrobial treatment with regular visits (e.g. every 1-4 months) until resolution of the lymphadenitis.

2.3 Ethics

The study protocol was approved, and institutional research permission was granted by the Department of Otorhinolaryngology, Helsinki University Hospital, Helsinki, Finland.

3. Results

3.1 Patient demographics and clinical presentation

We identified 52 patients (33 female and 19 male) with cervicofacial NTM lymphadenitis who met the inclusion criteria (Table 1). The median age at time of initial presentation was 2.9 years (Figure 1). The median parent-reported duration of symptoms until the first contact at our hospital was 25

days. Most of the patients (n=40) were seen by both a pediatrician and a specialist in ORL. The most affected nodal region was the upper neck/chin (levels I-II). No lymph node manifestations other than cervicofacial lymph node manifestations were presented. Histological sample was available for 24 patients (46%), and the most common finding was granulomatous infection. The median active follow-up was 8.2 months. During this time the patients were seen at the outpatient clinic six times on average. The passive follow-up time was 3.7 years (until May 31, 2018).

3.2 Microbiological culture and modified T-SPOT.TB $INF-\gamma$ release assay test

A sample for mycobacterium culture from the infected lymph node (drainage or tissue sample) was available from 34 (65%) of the patients. Cultures yielded NTM in 19 of the cases and an unspecified acid-fast rod in one case. Detected species were *Mycobacterium avium* (15 children), *M. malmoense* (2 children), *M. interjectum* (1 child), *M. intracellulare* and *M. simiae* (1 child). Altogether 49 patients (94%) were tested with the modified T-SPOT.TB test. All of them had a positive reaction on PPD stimulation and negative reactions on MTB-specific antigens indicative of NTM infection. The three patients not tested with the modified T-SPOT.TB had an NTM isolation in mycobacterial cultures.

3.3 Clinical course, observation group

Initial treatment was observation alone for 33 (63%) patients. Of these, nine patients (27%) did not develop a skin fistula, and the lymphadenitis resolved without drainage (Table 2). A fine needle biopsy (FNB) was obtained from 14 patients through intact skin for bacterial culture and cytologic analysis. After FNB, fistulization did not occur in three patients, ten patients had drainage, and for one patient there is no data available regarding fistula formation (Table 2). Drainage via fistula was mostly intermittent; some drainage appeared for days between longer periods without drainage. The

maximum time for intermittent drainage was one year. The NTM species did not seem to affect the drainage duration or fistula development; *M. avium* was the most common species, found in patients presenting at both ends of the clinical healing process (Table 2).

Of the 33 patients in the observation alone group, only one patient had scarring, which later needed surgical treatment for esthetic reasons. Another patient had recurrent lymph node swelling and the lymph node was later removed surgically.

3.4 Surgery group

Surgical intervention was performed on 19 patients (37% of all the study patients); in 6 patients the affected lymph node(s) were excised and 13 were treated with incision and curettage (Table 3).

Incision and curettage was performed in order to empty large draining lymph node to shorten the duration of drainage, or if bacterial or histological specimen was needed from a lymph node with indurated skin, but the risk of surgical complication would have been high for excision of the whole lymph node. After small incision to indurated skin the curettage was done with a small scoop to remove soft, necrotic tissue inside the lymph node without puncturing the capsule.

Two patients had more than one operation; one patient had excision of three lymph nodes first and later incision and curettage, and another patient had curettage twice. Two patients had postoperative infection and one patient postoperative hematoma. No complications affecting the function of the facial nerve were seen. Patients treated with excision presented no post-operative drainage. In curettage group, drainage lasted up to two months in seven patients, two patients had drainage more than two months and one more than six months. Three patients had no drainage. The number of patients was too small for any statistical analysis, but the dispersion of the drainage duration was similar in the curettage group compared to the observation group.

4. Discussion

The current treatment protocol of childhood NTM lymphadenitis, surgery or observation alone, has been in use for last ten years in our hospital. This retrospective study revealed that most of our patients (n=33, 63%) had been observed only without antimicrobial therapy and the lymphadenitis resolved spontaneously without complications. Although prolonged drainage lasting for months is feared consequence in NTM lymphadenitis, in our observation group in 14 children (42%) the drainage was minimal (less than two weeks) or none.

Our patient demographics compare well with those reported earlier. NTM lymphadenitis mostly affects children of under school age.^{2,7} For an unknown reason, females are over-represented in our cohort, as also reported earlier from Finland and other countries.^{1,8-11}

Previously, BCG vaccination coverage in Finland was excellent (>98%) and childhood NTM lymphadenitis was extremely rare.¹ At the time the change in BCG vaccination program took place NTM infections were unfamiliar to the clinicians. Therefore, the diagnosis was challenging and biopsies were performed as a routine part of the investigations. After adoption of the modified T-SPOT.TB test as a diagnostic tool for NTM lymphadenitis, the need for biopsies quickly diminished. This novel blood test has been essential for noninvasive diagnostics and dramatically changed our diagnostic and treatment protocols; the diagnosis can be achieved in few days after which the treatment outlines can be discussed with the parents.

Bacterial culture is still considered the gold standard diagnostic test for NTM infections, but limited by slow growth and poor sensitivity.¹² Novel techniques such as the 16S ribosomal RNA sequencing can increase the sensitivity and expedite the isolation from clinical specimens.¹³ Nevertheless, specimen collection usually requires invasive sampling. Noninvasive immunodiagnostic assays with different antigens have shown promising results, but remain commercially and widely unavailable.^{6,12,14} Prospective studies are required to further validate and facilitate wider adoption of these noninvasive diagnostic tests for childhood NTM lymphadenitis.

It is commonly assumed that the natural course of NTM lymphadenitis includes fistulization and drainage, typically lasting for months. In our data, however, 27% of the patients in the observation group did not develop a fistula, and the majority with a fistula had intermittent secretions for only days or weeks. Due to the novel blood test, and low TB incidence in Finland, invasive FNB was avoidable in most case. In an observational cohort study where FNB was part of the diagnostic protocol, fistulization rate was 97%.⁴ It has been speculated whether a puncture through intact skin could contribute to fistulization. In our study, a small difference was observed in fistulization between the groups with or without FNB (79% vs. 68%, respectively). In some patients, the reported fistulization may have initiated several weeks after FNB. Therefore, clear causality between FNB and fistula formation could not be determined.

In some cases incision and curettage was performed in order to empty surgically a large lymph node which had already indured the skin and was draining, but the area of the indured skin was wide and the location of the lymph node was such that removal of the whole lymph node would have been excessive and pose a high risk of complication. Our clinical experience suggests that if we are able to remove necrotic tissue from the lymph node, there is less tissue to drain which may shorten the draining period. The distribution of draining period was similar comparing the curettage group to observation group, but the number of patients were too small and curettage group too heterogenic for statistical analysis. A prospective study with larger population would be needed to study whether curettage will significantly shorten the drainage.

Patients included in the study underwent surgery for various reasons; to obtain a bacterial or histological specimen, as a curative treatment, or as a treatment for prolonged drainage. Thus, the surgery group was heterogenic. If the surgical treatment was deemed excessive (i.e. several affected lymph nodes) or if the risk of the facial nerve damage high, surgery was not performed. Parental opinion also affected the treatment choice. Parental involvement in the treatment decision process is important; a holistic approach should include education of the whole family about this non-severe

infection and its natural course. We recommend that the ORL specialist and parents decide on surgical treatment together unless there is a medical reason for or against surgery. We have not collected qualitative data on how the treatment, fistulization and duration of drainage effected the quality of life of the families. In general, our impression is that many parents prefer follow-up over surgery and the families cope well with the symptoms when given sufficient information, regular follow-up visits, and the possibility to get in touch with the treating clinician if needed. A recent report from Israel supports this view.¹⁵ In low-incidence settings, centralizing children with NTM lymphadenitis is beneficial and improves communication between different specialties.

5. Conclusion

Our current treatment protocol of childhood NTM lymphadenitis, surgery or observation alone, seems to be applicable also in the future. This study has shown that there were no major complications in either of the groups, and the majority of our patients in the observation group did not have excessive or prolonged drainage.

Due to the tedious nature of the disease and diagnostic uncertainty, childhood NTM lymphadenitis can cause concern for the family as well as the clinician. Nevertheless, *primum non nocere* – above all, do no harm. After instituting the novel blood-based test to our diagnostic scheme, invasive investigations have become avoidable in the majority of cases. Furthermore, when deciding on the treatment approach, preventing major complications such as facial paresis must be a priority.

Careful assessment and selection of patient that undergo surgery is crucial. Excision is an effective treatment in selected patients, but treating NTM lymphadenitis with observation alone, i.e. no antibiotics, is a good alternative to surgery. Informing the family about the natural course of the infection is essential.

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Table 1. Clinical characteristics, diagnostic methods, and treatment of children with cervicofacial nontuberculous mycobacteria (NTM) lymphadenitis.

	No.	%†
Total no. of patients	52	100
Female	33	63
Age at presentation, years, median (range)	2.9 (1.1-7.1)	
Duration of symptoms before the first contact, days, median (range)	25 (1-130)	
Treating speciality		
Pediatrics	5	10
ENT	7	13
Both	40	77
Location of the infected lymphnodes		
Facial	7	13
Upper neck/chin	23	44
Mid/lower neck	16	31
Multifocal lesions	6	12
Method of NTM diagnosis‡		
Culture and T-SPOT.TB positive	17	33
Culture positive, T-SPOT.TB not analyzed	3	6
Culture negative, T-SPOT.TB positive	14	27
No culture, T-SPOT.TB positive	18	35
Histological examination performed	24	46
Treatment		

Surgery	19	37
Observation	33	63
Follow-up, median		
Active, months	8.2	
Passive, years‡	3.7	
Visits to hospital, median (range)		
Total	6 (1-15)	
Surgery group	8 (3-15)	
Observation group	5 (1-15)	

† % of all 52 study patients

‡ Up until May 31st 2018

Table 2. Duration of (intermittent) drainage and involvement of fine needle biopsy of children infected by nontuberculous mycobacteria (NTM) in the observation-only group.

	Fine needle biopsy obtained		No fine needle biopsy		Total (%) [†]
Duration of drainage	No. [‡]	NTM species	No.	NTM species [§]	
None	3	1 <i>M. avium</i> , 2 insufficient sample	6	nd	9 (27%)
< 2 weeks	1	1 <i>M. malmoense</i>	4	nd	5 (15%)
2 weeks –2 months	4	1 <i>M. avium</i> , 1 acid fast rod, 2 negative	4	1 <i>M. malmoense</i> , 1 negative, 2 nd	8 (24%)
2–6 months	3	2 <i>M. avium</i> , 1 negative	4	1 <i>M. avium</i> , 3 negative	7 (21%)
6-12 months	2	2 <i>M. avium</i>	0		2 (6%)
Not determined	1	1 <i>M. avium</i>	1	nd	2 (6%)
Total	14		19		33 (100%)

[†] % Percentage of all patients in the observation-only group

[‡] No. of patients

[§] Bacterial culture was obtained from the draining fistula

nd = not determined, no samples for culture available

Table 3. Choice of treatment, complications, and duration of drainage of children with nontuberculous mycobacteria lymphadenitis treated with surgery.

	Incision and curettage No. of patients (%)	Excision† No. of patients (%)
Initial surgery	13	6
Re-operation	1	1
Postoperative infection or hematoma	0	3
Duration of drainage after surgery		
None	3 (23%)	4 (67%)
< 2 weeks	3 (23%)	2 (33%)‡
2 weeks –2 months	4 (31%)	0
2–6 months	2 (15%)	0
6-12 months	1 (8%)§	0

† Excision of the whole lymph node(s)

‡ One postoperative hematoma and one drainage after second operation (curettage)

§ Curettage was done twice because of prolonged secretion

